

REMARKS

Claims 17-20 were under consideration. Claim 17 has been amended. Accordingly, claims 17-20 will remain pending in the application. Applicants have amended the first paragraph of the application in order to correct the priority information.

Amendment to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in another patent application.

Rejection of Claims 17-20 Based on Obviousness-Type Double Patenting

Claims 17-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Application No. 09/157,748 (now U.S. Patent No. 6,461,813) or over application S.N. 09/062,330 for reasons of record.

Applicants respectfully traverse the foregoing rejection. However, at such time as the subject matter of the instant application is indicated allowable, Applicants will terminally disclaim the corresponding claims of the present application.

Rejection of Claims 1-7 under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1-7 under 35 U.S.C. §103 (a) "as being obvious over Application No. 09/157,748 (now U.S. 6,461,813) which has a common inventor with the instant application for reasons advanced in last Office action."

Applicants respectfully submit that claims 1-7 were canceled in the previous Amendment and Response, filed January 17, 2002, thereby rendering the foregoing rejection moot.

Rejection of Claims 17-20 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 17-20 under 35 U.S.C. §112, first paragraph, because “the specification, while being enabling for a method specific for the p21 as the bioactive agent that modulates a specific tumor cell, does not reasonably provide enablement for a method using a library of any bioactive agents or nucleic acid that encodes said bioactive agents that modulates any population of cells.” In response to Applicants arguments set forth in the previous Amendment and Response, filed January 17, 2002, the Examiner states that

it is not the definition of the candidate bioactive agent that is at issue. Rather, the scope of the candidate agent encoded by a population of retroviral vectors. As stated by applicants above, the candidate bioactive agents include numerous types of agents in the modified and unmodified state. These agents of unknown constitution when made into a library may not provide a true representation of the candidate agents in the library. It is not therefore apparent from the enabling disclosure which bioactive agent can be considered candidate to affect the cell phenotype. Mere recitation of a method with any agent without knowing how the agent manipulatively affects the cell phenotype entails undue experimentation. There are too numerous undefined variables for one skilled in the art to determine in order to practice the claimed invention.

The Examiner has suggested that applicants amend the claims to recite a method to the use of library of p21 and its mutants as the bioactive agents in tumor cell populations.

Applicants respectfully traverse the foregoing rejection. The pending claims are directed to a method of screening for an alteration in cellular phenotype comprising providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents; sorting said population of cells based on at least five parameters using fluorescence activated cell sorting (FACS); and detecting at least one cell of said population having said alteration in said cellular phenotype wherein said cellular phenotype is selected from a group of cellular phenotypes consisting of cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene.

Applicants respectfully submit that Applicants' specification provides a large number of examples of candidate agents which may be used in the methods of the invention, as well as methods and sources for obtaining and producing these candidate agents (see, for example, page 16, line 8 through page 30, line 15). In particular, the instant invention includes providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents for use in the claimed methods. Applicants' specification provides detailed description of making and using libraries of retroviral vectors encoding candidate bioactive agents and methods for introducing these vectors into cells (see, for example page 19, line 31 through page 31, line 4). Thus, Applicants' disclosure, in combination with information known in the art at the time the application was filed regarding the preparation of libraries of candidate agents, would enable one of ordinary skill in the art to carry out the claimed methods without undue experimentation.

Furthermore, Examiner is of the opinion that "to select and determine the various agents that would affect a cell phenotype in five different ways amounts to an invitation to experiment. Before measurement of even a single effect is achieved, one has to identify the source (agent) that causes the different cellular phenotype parameters." With respect to this statement, Applicants respectfully point out that the instantly claimed methods are used to identify compounds that have a desired effect on preselected parameters to be measured. The methods of the invention do not require that the "agent that causes the different cellular phenotype parameters" be identified prior to performing the assay. In fact, the purpose of the assay is to identify the agent which causes an effect on cellular phenotype, as determined by sorting the cells based on at least five different parameters, *i.e.*, cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene. For the purposes of such an assay, it

is not required that the identity of a candidate agent be known at all, let alone prior to performing the assay.

In addition, Applicants submit that the Patent Office has recognized that screening assay claims having no limitation as to the compounds to be tested are patentable (see, for example U.S. Patent No. 6,461,813, which was cited by the Examiner in the instant Office Action).

Accordingly, Applicants respectfully submit that the claims are fully enabled by Applicants' specification and request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 17-20 Under 35 U.S.C. §103

The Examiner has rejected claims 17-20 under 35 U.S.C. §103 (a) as being obvious over Nolan (WO 97/27212) in view of Kamb "for reasons advanced in the last Office action."

In particular, the Examiner is of the opinion that

Nolan provides a list for the effective isolation of bioactive agents that affect cell phenotype. The suggested teaching in the list of Nolan suffices the finding of obviousness. Attention is directed at e.g., Example 1, line 23 up to page 52, line 2 wherein the cells after washing is transferred to Fluorescent activated cell sorting (FACS) tube for analysis which shows expression of Bcl2 (expression of cell surface receptor, as claimed) from retroviral promoter that inhibits apoptosis. FACS machine are known to measure optical properties like (1) fluorescence which would indicate that the cell is (2) viable and that the agent inhibit (3) apoptosis. [Note page 1, lines 26-28 of the instant specification which recites the known fact that FACS is used to sort individual cells on the basis of optical properties, including fluorescence.].

Kamb, as stated in the last Office action teaches the use of FACS to separate cells based on the expression of a single reporter gene. The population of cells is sorted based on expression of a reporter gene. Kamb refers to GFP as a vital dye that refers to the fact that the GFP is expressed without killing the cell. Kamb discloses the sorting of the single expressed gene by sorting the cells based on the different cellular parameters of (1) a fluorescently labeled antibody (i.e., immunofluorescence); (2) quantifying measurement level of the expressed reporter gene (e.g., col.8, line 45 up to col. 9, line 7) and (3) the uptake of the GFP (a "vital dyes") or its emission or (4) the use of BFP.

Applicants respectfully traverse the foregoing rejection. The pending claims are directed to methods of screening for an alteration in cellular phenotype comprising providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents; sorting said population of cells based on at least five parameters using fluorescence activated cell sorting (FACS); and detecting at least one cell of said population having said alteration in said cellular phenotype wherein said cellular phenotype is selected from a group of cellular phenotypes consisting of cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene.

The instant invention is based on the *sorting cells based on at least five parameters* using FACS and detecting a cell with an altered cellular phenotype, wherein the phenotype is selected from the group consisting of *cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene*. Sorting cells based on multiple parameters is beneficial in that, by assaying a variety of cellular parameters by FACS, rapid and accurate screening may be carried out. Evaluation of multiple parameters results in reduced background and greater specificity. Moreover, a major benefit of screening based on multiple parameters is the marked reduction in false positives. FACS has been previously used to evaluate two different or unrelated characteristics at the same time which identifies cells having those two characteristics, but does not reduce the background for the combined characteristics. While FACS is capable of identifying various parameters, the convention at the time of filing the instant application was to sort cells based on a single, or, at most, a pair of parameters of interest. In hindsight, screening on the basis of multiple parameters for reducing false positives may seem obvious. However, at the time the invention was made, it was conventional to sort based on a limited number of parameters and perform further experimentation to characterize the sorted cells using methods other than FACS. The present

methods result in a great reduction in post-sorting experimentation, allowing for increased efficiency in discovering novel agents that modulate cellular phenotype.

The Nolan Reference

The Nolan reference broadly discusses methods for isolating a cell having an altered phenotype from a plurality of other cells (*see, e.g.*, page 33, lines 19-28 of the Nolan reference). For example, Nolan discloses that “standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, including FACS” by be used in detecting an altered cellular phenotype (page 31, line 32 through page 32, line 1 of the Nolan reference). Nolan also describes the use of FACS to measure β -gal expression (page 76, lines 14-21), lacZ expression (page 28, lines 27-30), and to select for cells that “induce VCAM or ICAM-1 expression after IL-1 signaling” (page 79, lines 18-20).

There is no teaching or suggestion in Nolan, et al. to do multiple analyses let alone measuring *at least five parameters* to identify an alteration in cellular phenotype, wherein the cellular phenotype is selected from the following: *cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene*. Nolan refers to only to assaying a single phenotype per assay. Applicants respectfully submit that the Examiner has failed to identify any teaching or suggestion in Nolan of sorting cells based on *at least five parameters*. The Examiner points to Example 1 of Nolan. However, Applicants respectfully submit that Example 1 does not describe the sorting of cells based on at least five parameters. Rather, Example 1 describes the screening of cells based on the fluorescence of fluorescein labeled dUTP. Furthermore, Nolan does not teach or suggest *providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents* and sorting the cells based on at least five parameters using FACS.

Accordingly, Nolan fails to teach or suggest each and every element of the claimed invention.

The Kamb Reference

The Kamb reference fails to make up for the deficiencies of the Nolan reference. The Kamb reference describes methods of screening for perturbagens which can interfere with specific biochemical processes in a cell and affect a specific cellular phenotype. The method includes the use of reporter gene which whose level of expression correlates with the phenotypic state of the cell. Kamb describes the use of a FACS device to screen cells to identify those with a particular phenotype. Namely, Kamb discloses that FACS may be used to analyze reporter gene, *e.g.*, GFP, expression. Kamb also teaches repeated screening/selection process for sorting cells other than the measurement of multiple parameters in the assay.

Kamb does not teach or suggest ***providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents*** and sorting the cells based on ***at least five parameters*** using FACS to ***identify an alteration in cellular phenotype***.

Thus, none of the cited references, alone or in combination, teaches screening for methods of screening for an alteration in cellular phenotype comprising providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents; sorting said population of cells based on at least five parameters using fluorescence activated cell sorting (FACS); and detecting at least one cell of said population having said alteration in said cellular phenotype wherein said cellular phenotype is selected from a group of cellular phenotypes consisting of cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene. Therefore, the prior art references in combination do not teach

or suggest all the claim limitations as required by M.P.E.P. 2143. Accordingly, the claims are not obvious in view of the cited art.

Furthermore, even if the cited art taught all the claim limitations, which Applicants deny, Applicants maintain that at the time the invention was made, the prior art failed to provide sufficient motivation to modify the teachings of the primary references to arrive at the claimed invention. With respect to motivation to make the claimed invention, the Examiner has failed to set forth adequate evidence of a motivating force which would have impelled one of ordinary skill in the art to modify the teachings of the references to arrive at the claimed invention. In support of their position, Applicants point to the CAFC decision in *In re Rouffet*, (149 F.3d 1350) (Fed. Cir. 1998)). Rouffet filed a patent application directed to technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites. Rouffet taught changing the shape of the beam transmitted by the satellite's antenna to a fan-shaped beam. The Examiner rejected Rouffet's claims as unpatentable over U.S. patent number 5,199,672 (King) in view of U.S. Patent number 4,872,015 (Rosen) and a report titled "A Novel Non-Geostationary Satellite Communications System" (Ruddy). The CAFC found that:

[although] the board did not err in finding that the combination of King, Rosen, and Ruddy contains all of the elements claimed in Rouffet's application. . .the Board reversibly erred in determining that one of skill in the art would have been motivated to combine these references in a manner that rendered the claimed invention obvious. Indeed, the Board did not identify any motivation to choose these references for combination.

Similarly, it is Applicants' position that the Examiner has failed to point to any motivation to ***provide a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents*** and to sort cells based on ***at least five parameters to detect a cell having an alteration in cellular phenotype, wherein said cellular phenotype is selected***

from: cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene, as presently claimed. In *Rouffet* the Court of Appeals continued:

[b]ecause the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. See *In re Gorman*, 933 F.2d 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen, and Ruddy. *In re Rouffet* at [*17].

Neither Nolan nor Kamb *et al.* ***teach or suggest assaying at least five parameters to detect an alteration in cellular phenotype***. Thus, there is no motivation to modify the teachings of Nolan to measure additional parameters in order to optimize screening for agents which alter cellular phenotype.

Since the Examiner has not pointed to any teaching or suggestion in the art that would have impelled the ordinarily skilled artisan to modify the cited art to arrive at the screening methods claimed, it is Applicants' position that the Examiner has used Applicants' invention as a blueprint to combine the references. The CAFC has ruled that "[a] holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be 'contrary to statute and would defeat the congressional purpose in enacting Title 35.' "

SmithKline Diagnostics, 859 F.2d. at 886-887 (citing *Panduit Corp v. Dennison Mfg. Co.*, 810 F.2d 1561, 1577 (Fed. Cir. 1987)) (citations omitted).

In view of the foregoing, Applicants respectfully submit that the claimed invention is not obvious over the art of record. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of the pending claims under 35 U.S.C. §103.

The Examiner has also rejected claims 17-20 under 35 U.S.C. §103(a) as being unpatentable over either Nolan in view of Kamb and further in view of Hide et al (Jrnl. of Cell Biology) “for reasons advanced in the last Office action.”

In particular, the Examiner is of the opinion that

Hide is combined with Nolan and Kamb for the its teaching as to the cellular phenotype, exocytosis and measuring said cellular parameter to detect the forward and light scattering of cells to show the exocytosis effect of the cells. This attribute has been used to classify populations of (mast) cells. Thus, applicants cannot attack the references individually when the rejection is based on the combination of references.

Applicants respectfully traverse the foregoing rejection. Nolan and Kamb are discussed above. The Hide *et al.* reference fails to cure the deficiencies in the teachings of the Nolan and Kamb references. Hide *et al.* investigate the relationship between the extent of secretion from mast cells (assessed as the release of hexosaminidase) and the degranulation (exocytosis) responses of individual cells. Hide *et al.* describe the use of light scatter in flow cytometry to examine degranulation in mast cells.

Hide *et al.* do not teach a screening assay to identify alterations in cellular phenotype. The Hide reference is simply directed to classifying cell populations. Furthermore, Hide *et al.* do not teach or suggest assaying multiple parameters of a cell using FACS analysis, let alone assaying for five of the recited parameters in combination. Accordingly, Hide, in combination with Nolan and Kamb, fail to teach each and every limitation of the claimed invention.

Furthermore, even if the cited art taught all the claim limitations, which Applicants deny, Applicants maintain that at the time the invention was made, the prior art failed to provide sufficient motivation to modify the teachings of the primary references to arrive at the claimed

invention. With respect to motivation to make the claimed invention, the Examiner has failed to set forth adequate evidence of a motivating force which would have impelled one of ordinary skill in the art to modify the teachings of the references to arrive at the claimed invention.

The Examiner is of the opinion that “[o]ne having ordinary skill in the art would have been motivated to measure another cellular parameters as light scattering by FACS when the cellular phenotype is caused by exocytosis to provide a clear or discernible effect of the cells.”

Applicants respectfully submit that there is no motivation in Nolan, Kamb, or Hide to sort cells based on any additional parameters in order to identify an alteration in cellular phenotype.

Furthermore, with respect to the Examiner’s statement that “it is well known the overall performance of the combination is always equal to the sum of the functions of the individual components.” Applicants respectfully submit there is no indication in the teachings of Nolan, Kamb, or Hide that sorting cells with multiple parameters would be beneficial or advantageous compared to the methods used by Nolan, Kamb, or Hide. Thus, these references provide no motivation to carry out the claimed methods using at least five parameters.

In view of the foregoing, Applicants respectfully submit that the claimed invention is not obvious over the art of record. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of the pending claims under 35 U.S.C. §103.

CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400. Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. RGV-006CPRCE from which the undersigned is authorized to draw.

Dated: **September 24, 2004**

Respectfully submitted,

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